

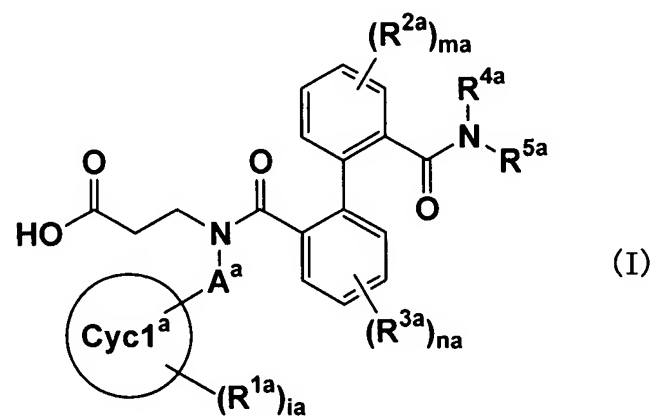
AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings of claims in the application:

LISTING OF CLAIMS:

1. - 6. (canceled)

7. (currently amended): A method for the treatment ~~and/or prevention~~ of a chronic disease selected from the group consisting of chronic asthma, glomerular nephritis, obesity, prostate hyperplasia, a disease induced by the progress of arteriosclerosis, and rheumatoid or atopic dermatitis, wherein said method ~~which~~ comprises administering to a mammal having said chronic disease an effective amount of an EDG-2 antagonist,
wherein the EDG-2 antagonist is a β -alanine derivative of formula (I)



wherein A^a is, (1) C1-6 alkylene, (2) C2-6 alkenylene, or (3) C2-6 alkynylene, wherein

A^a may be substituted with 1-3 of C1-4 alkyl,

Cyc1^a is, (1) C3-15 carboring, or (2) 3-15 membered heteroring having 1-4 of nitrogen,

1-2 of oxygen and/or 1-2 of sulfur,

R^{1a} is (1) C1-4 alkyl, (2) halogen, (3) cyano, (4) trihalomethyl, (5) -OR^{6a}, (6) -SR^{7a},

(7) -NR^{8a}R^{9a}, (8) nitro, (9) -COOR^{10a}, (10) -CONR^{11a}R^{12a}, (11) -NR^{13a}COR^{14a},

(12) -SO₂NR^{15a}R^{16a}, (13) -NR^{17a}SO₂R^{18a}, (14) -S(O)R^{19a}, or (15) -SO₂R^{20a},

R^{6a}, R^{7a}, R^{8a}, R^{9a}, R^{10a}, R^{11a}, R^{12a}, R^{13a}, R^{14a}, R^{15a}, R^{16a}, R^{17a}, R^{18a}, R^{19a} and R^{20a} are each

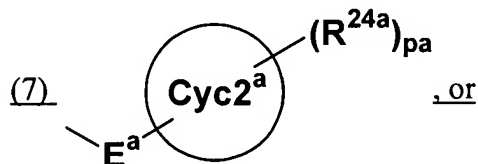
independently, (1) hydrogen, or (2) C1-4 alkyl,

R^{2a} and R^{3a} are each independently, (1) C1-4 alkyl, (2) C1-4 alkoxy, or (3) halogen,

R^{4a} and R^{5a} are each independently, (1) hydrogen, (2) C1-4 alkyl, (3) C2-4 alkenyl,

(4) C2-4 alkynyl, (5) C1-4 alkyl substituted with -OR^{21a}, (6) C1-4 alkyl substituted with

-NR^{22a}R^{23a} or



R^{4a} and R^{5a} are taken together with the nitrogen to which they are attached to form a 3-15
membered mono-, bi- or tri-cyclic heteroring, wherein the heteroring represents at least one
nitrogen and it may be substituted with C1-4 alkyl substituted with -OR^{25a},

R^{21a}, R^{22a}, R^{23a} and R^{25a} are each independently, (1) hydrogen, (2) C1-4 alkyl, (3) C2-6 acyl, or (4) trihaloacetyl,

E^a is (1) a bond, (2) C1-6 alkylene, (3) C2-6 alkenylene, or (4) C2-6 alkynylene, wherein E^a may be substituted with 1-3 of (1) C1-4alkyl, or (2) C1-4 alkyl substituted with -OR^{26a},

R^{26a} is (1) hydrogen, (2) C1-4 alkyl, (3) C2-6 acyl, or (4) trihaloacetyl, Cyc2^a is (1) C3-15 carboring, or (2) 3-15 membered heteroring having 1-4 of nitrogen, 1-2 of oxygen and/or 1-2 of sulfur,

R^{24a} is (1) C1-4 alkyl, (2) halogen, (3) cyano, (4) trihalomethyl, (5) -OR^{27a}, (6) -SR^{28a}, (7) -NR^{29a}R^{30a}, (8) nitro, (9) -COOR^{31a}, (10) -CONR^{32a}R^{33a}, (11) -NR^{34a}COR^{35a}, (12) -SO₂NR^{36a}R^{37a}, (13) -NR^{38a}SO₂R^{39a}, (14) -S(O)R^{40a}, or (15) -SO₂R^{41a},

R^{27a}, R^{28a}, R^{29a}, R^{30a}, R^{31a}, R^{32a}, R^{33a}, R^{34a}, R^{35a}, R^{36a}, R^{37a}, R^{38a}, R^{39a}, R^{40a} and R^{41a} are each independently (1) hydrogen, or (2) C1-4 alkyl,

ia is 0 or an integer of 1 to 5, ma is 0 or an integer of 1 to 4, and

na is 0 or an integer of 1 to 4, pa is 0 or an integer of 1 to 5, and

wherein when ia is 2 or more, R^{1a}'s are the same or different,

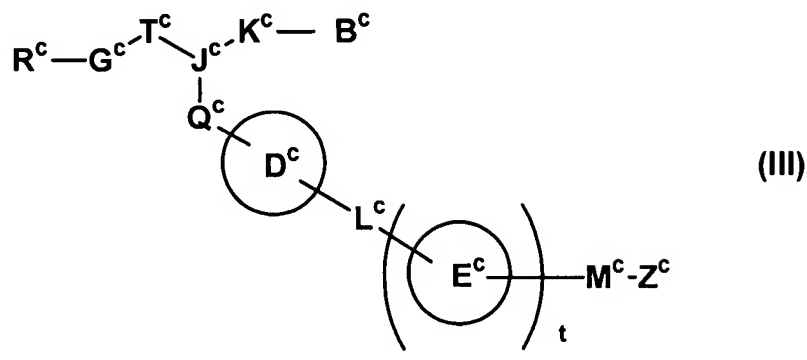
when ma is 2 or more, R^{2a}'s are the same or different,

when na is 2 or more, R^{3a}'s are the same or different, and

when pa is 2 or more, they are the same or different, or

a prodrug thereof or a salt thereof;

or the EDG-2 antagonist is a compound of formula (III)



wherein R^c is optionally substituted aliphatic hydrocarbon or a ring group optionally having substituent(s),

G^c is a bond or a spacer having a main chain of 1 to 8 atoms,

T^c is $-CH_2-$ or a spacer having a main chain of 1 atom having a hydrogen bond-accepting group optionally having substituent(s),

J^c is nitrogen or carbon,

B^c is optionally substituted aliphatic hydrocarbon or a ring group optionally having substituent(s),

K^c is (1) a bond or (2) a spacer having a main chain of 1 to 8 atoms which may form a ring together with the substituent of the ring group represented by R^c , ring D^c or the substituent of the ring D^c ,

Q^c is (1) a bond or (2) a spacer having a main chain of 1 to 8 atoms which may form a ring together with the ring group represented by R^c , a substituent of the ring group represented by R^c , or K^c ,

ring D^c is a ring optionally having more substituent(s),

L^c is a bond or a spacer having a main chain of 1 to 3 atoms,

ring E^c is, a ring group optionally having substituent(s),

M^c is a bond or a spacer having a main chain of 1 to 8 atoms,

Z^c is an acidic group, and

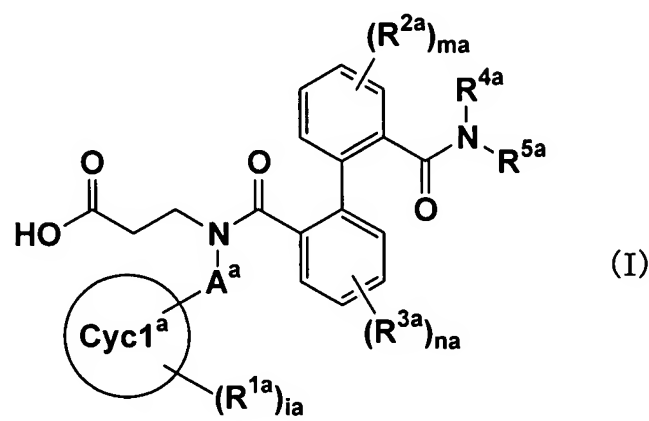
t is 0 or 1, or

a salt thereof.

8. (canceled).

9. (currently amended) A pharmaceutical composition~~remedy and/or preventive of~~
~~a chronic disease~~, comprising an EDG-2 antagonist in combination with one or more selected
from LPA receptor antagonist, anti-androgenic agent, $\alpha 1$ receptor blocker or 5α -reductase
inhibitor,

wherein the EDG-2 antagonist is a β -alanine derivative of formula (I)



wherein A^a is, (1) C1-6 alkylene, (2) C2-6 alkenylene, or (3) C2-6 alkynylene, wherein
A^a may be substituted with 1-3 of C1-4 alkyl,

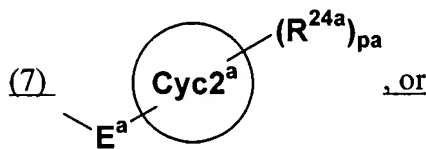
Cyc1^a is, (1) C3-15 carboring, or (2) 3-15 membered heteroring having 1-4 of nitrogen, 1-2 of oxygen and/or 1-2 of sulfur,

R^{1a} is (1) C1-4 alkyl, (2) halogen, (3) cyano, (4) trihalomethyl, (5) -OR^{6a}, (6) -SR^{7a}, (7) -NR^{8a}R^{9a}, (8) nitro, (9) -COOR^{10a}, (10) -CONR^{11a}R^{12a}, (11) -NR^{13a}COR^{14a}, (12) -SO₂NR^{15a}R^{16a}, (13) -NR^{17a}SO₂R^{18a}, (14) -S(O)R^{19a}, or (15) -SO₂R^{20a},

R^{6a}, R^{7a}, R^{8a}, R^{9a}, R^{10a}, R^{11a}, R^{12a}, R^{13a}, R^{14a}, R^{15a}, R^{16a}, R^{17a}, R^{18a}, R^{19a} and R^{20a} are each independently, (1) hydrogen, or (2) C1-4 alkyl,

R^{2a} and R^{3a} are each independently, (1) C1-4 alkyl, (2) C1-4 alkoxy, or (3) halogen,

R^{4a} and R^{5a} are each independently, (1) hydrogen, (2) C1-4 alkyl, (3) C2-4 alkenyl, (4) C2-4 alkynyl, (5) C1-4 alkyl substituted with -OR^{21a}, (6) C1-4 alkyl substituted with -NR^{22a}R^{23a} or



R^{4a} and R^{5a} are taken together with the nitrogen to which they are attached to form a 3-15 membered mono-, bi- or tri-cyclic heteroring, wherein the heteroring represents at least one nitrogen and it may be substituted with C1-4 alkyl substituted with -OR^{25a},

R^{21a}, R^{22a}, R^{23a} and R^{25a} are each independently, (1) hydrogen, (2) C1-4 alkyl, (3) C2-6 acyl, or (4) trihaloacetyl,

E^a is (1) a bond, (2) C1-6 alkylene, (3) C2-6 alkenylene, or (4) C2-6 alkynylene, wherein E^a may be substituted with 1-3 of (1) C1-4alkyl, or (2) C1-4 alkyl substituted with -OR^{26a},

R^{26a} is (1) hydrogen, (2) C1-4 alkyl, (3) C2-6 acyl, or (4) trihaloacetyl, Cyc2^a is (1) C3-15 carboring, or (2) 3-15 membered heteroring having 1-4 of nitrogen, 1-2 of oxygen and/or 1-2 of sulfur,

R^{24a} is (1) C1-4 alkyl, (2) halogen, (3) cyano, (4) trihalomethyl, (5) -OR^{27a}, (6) -SR^{28a}, (7) -NR^{29a}R^{30a}, (8) nitro, (9) -COOR^{31a}, (10) -CONR^{32a}R^{33a}, (11) -NR^{34a}COR^{35a}, (12) -SO₂NR^{36a}R^{37a}, (13) -NR^{38a}SO₂R^{39a}, (14) -S(O)R^{40a}, or (15) -SO₂R^{41a},

R^{27a}, R^{28a}, R^{29a}, R^{30a}, R^{31a}, R^{32a}, R^{33a}, R^{34a}, R^{35a}, R^{36a}, R^{37a}, R^{38a}, R^{39a}, R^{40a} and R^{41a} are each independently (1) hydrogen, or (2) C1-4 alkyl,

ia is 0 or an integer of 1 to 5, ma is 0 or an integer of 1 to 4, and

na is 0 or an integer of 1 to 4, pa is 0 or an integer of 1 to 5, and

wherein when ia is 2 or more, R^{1a}'s are the same or different,

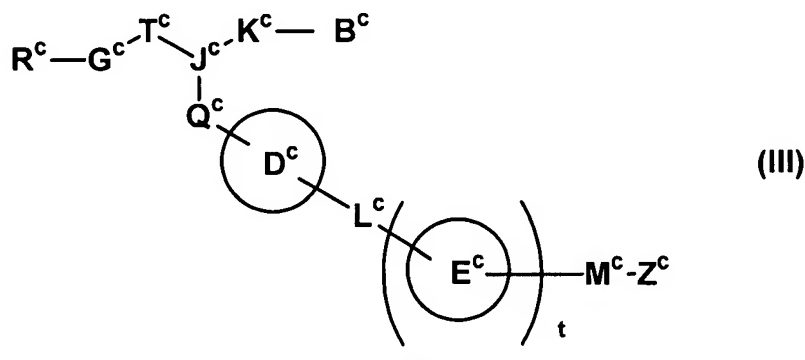
when ma is 2 or more, R^{2a}'s are the same or different,

when na is 2 or more, R^{3a}'s are the same or different, and

when pa is 2 or more, they are the same or different, or

a prodrug thereof or a salt thereof;

or the EDG-2 antagonist is a compound of formula (III)



wherein R^c is optionally substituted aliphatic hydrocarbon or a ring group optionally having substituent(s),

G^c is a bond,

T^c is -CH₂- or a spacer having a main chain of 1 atom having a hydrogen bond-accepting group optionally having substituent(s),

J^c is nitrogen or carbon,

B^c is optionally substituted aliphatic hydrocarbon or a ring group optionally having substituent(s),

K^c is (1) a bond or (2) a spacer having a main chain of 1 to 8 atoms which may form a ring together with the substituent of the ring group represented by R^c, ring D^c or the substituent of the ring D^c,

Q^c is (1) a bond or (2) a spacer having a main chain of 1 to 8 atoms which may form a ring together with the ring group represented by R^c, a substituent of the ring group represented by R^c, or K^c,

ring D^c is a ring optionally having more substituent(s),

L^c is a bond or a spacer having a main chain of 1 to 3 atoms,

ring E^c is selected from the group consisting of benzene optionally having substituent(s), piperidine optionally having substituent(s), isoxazole optionally having substituent(s), pyrazole optionally having substituent(s), pyridine optionally having substituent(s), thiazole optionally having substituent(s), imidazole optionally having substituent(s), pyrrole optionally having substituent(s), and pyrrolidine optionally having substituent(s),

M^c is a bond or a spacer having a main chain of 1 to 8 atoms,

Z^c is an acidic group, and

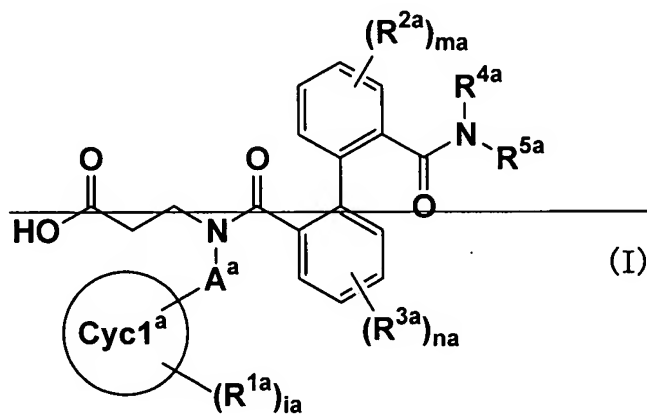
t is 0 or 1, or

a salt thereof.

10. (canceled).

11. (currently amended): The method according to claim ~~7~~10, wherein the chronic disease is prostate hyperplasia.

12. (currently amended): The method according to claim 7, wherein the EDG-2 antagonist is asaid β -alanine derivative of formula (I)



~~wherein A^a is, (1) C1-6 alkylene, (2) C2-6 alkenylene, or (3) C2-6 alkynylene, wherein A^a may be substituted with 1-3 of C1-4 alkyl,~~

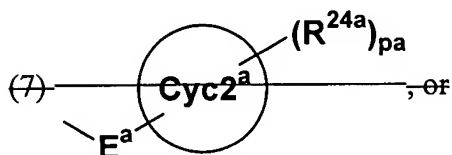
~~_____ Cyc1^a is, (1) C3-15 carboring, or (2) 3-15 membered heteroring having 1-4 of nitrogen,
1-2 of oxygen and/or 1-2 of sulfur,~~

~~_____ R^{1a} is (1) C1-4 alkyl, (2) halogen, (3) cyano, (4) trihalomethyl, (5) OR^{6a}, (6) SR^{7a};
(7) NR^{8a}R^{9a}, (8) nitro, (9) COOR^{10a}, (10) CONR^{11a}R^{12a}, (11) NR^{13a}COR^{14a},
(12) SO₂NR^{15a}R^{16a}, (13) NR^{17a}SO₂R^{18a}, (14) S(O)R^{19a}, or (15) SO₂R^{20a};~~

~~_____ R^{6a}, R^{7a}, R^{8a}, R^{9a}, R^{10a}, R^{11a}, R^{12a}, R^{13a}, R^{14a}, R^{15a}, R^{16a}, R^{17a}, R^{18a}, R^{19a} and R^{20a} are each
independently, (1) hydrogen, or (2) C1-4 alkyl,~~

~~_____ R^{2a} and R^{3a} are each independently, (1) C1-4 alkyl, (2) C1-4 alkoxy, or (3) halogen,~~

~~_____ R^{4a} and R^{5a} are each independently, (1) hydrogen, (2) C1-4 alkyl, (3) C2-4 alkenyl,
(4) C2-4 alkynyl, (5) C1-4 alkyl substituted with OR^{21a}, (6) C1-4 alkyl substituted with
NR^{22a}R^{23a} or~~



~~_____ R^{4a} and R^{5a} are taken together with the nitrogen to which they are attached to form a 3-15
membered mono-, bi- or tri-cyclic heteroring, wherein the heteroring represents at least one
nitrogen and it may be substituted with C1-4 alkyl substituted with OR^{25a};~~

~~_____ R^{21a}, R^{22a}, R^{23a} and R^{25a} are each independently, (1) hydrogen, (2) C1-4 alkyl, (3) C2-6
acyl, or (4) trihaloacetyl,~~

~~_____ E^a is (1) a bond, (2) C1-6 alkylene, (3) C2-6 alkenylene, or (4) C2-6 alkynylene, wherein
E^a may be substituted with 1-3 of (1) C1-4 alkyl, or (2) C1-4 alkyl substituted with OR^{26a};~~

~~_____R^{26a} is (1) hydrogen, (2) C1-4 alkyl, (3) C2-6 acyl, or (4) trihaloacetyl, Cyc2^a is (1) C3-15 carboring, or (2) 3-15 membered heteroring having 1-4 of nitrogen, 1-2 of oxygen and/or 1-2 of sulfur,~~

~~_____R^{24a} is (1) C1-4 alkyl, (2) halogen, (3) cyano, (4) trihalomethyl, (5) OR^{27a}, (6) SR^{28a}, (7) NR^{29a}R^{30a}, (8) nitro, (9) COOR^{31a}, (10) CONR^{32a}R^{33a}, (11) NR^{34a}COR^{35a}, (12) SO₂NR^{36a}R^{37a}, (13) NR^{38a}SO₂R^{39a}, (14) S(O)R^{40a}, or (15) SO₂R^{41a},~~

~~_____R^{27a}, R^{28a}, R^{29a}, R^{30a}, R^{31a}, R^{32a}, R^{33a}, R^{34a}, R^{35a}, R^{36a}, R^{37a}, R^{38a}, R^{39a}, R^{40a} and R^{41a} are each independently (1) hydrogen, or (2) C1-4 alkyl,~~

~~_____ia is 0 or an integer of 1 to 5, ma is 0 or an integer of 1 to 4, and~~

~~_____na is 0 or an integer of 1 to 4, pa is 0 or an integer of 1 to 5, and~~

~~_____wherein when ia is 2 or more, R^{1a}'s are the same or different,~~

~~_____when ma is 2 or more, R^{2a}'s are the same or different,~~

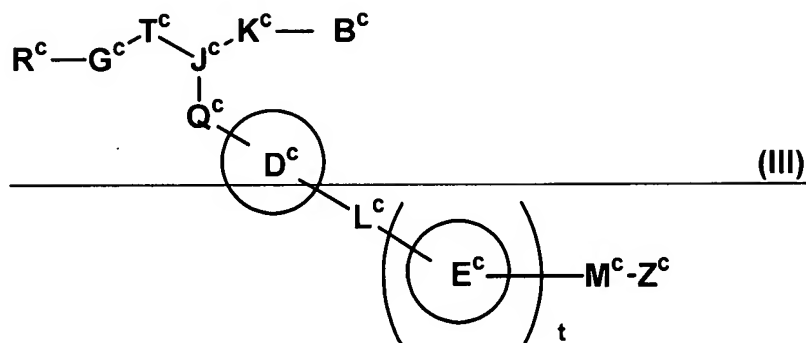
~~_____when na is 2 or more, R^{3a}'s are the same or different, and~~

~~_____when pa is 2 or more, they are the same or different, or~~

a prodrug thereof or a salt thereof.

13. (canceled).

14. (currently amended): The method according to claim 7, wherein the EDG-2 antagonist is saida compound of formula (III)



~~L⁶ is a bond or a spacer having a main chain of 1 to 3 atoms,~~

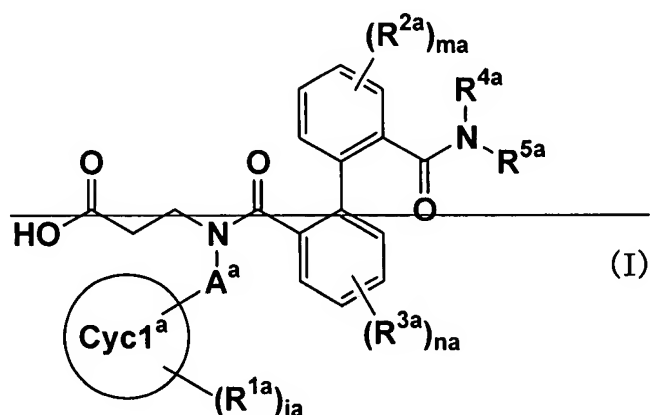
~~ring E⁶ is, a ring group optionally having substituent(s),~~
~~M⁶ is a bond or a spacer having a main chain of 1 to 8 atoms,~~
~~Z⁶ is an acidic group, and~~
~~t is 0 or 1, or~~
a salt thereof.

15. (currently amended): The method according to claim 7, wherein the method comprises administering to said mammal one or more members selected from the group consisting of an LPA receptor antagonist, an anti-androgenic agent, an α 1 receptor blocker, and an 5α -reductase inhibitor is used, in combination with the EDG-2 antagonist.

16. (currently amended): The pharmaceutical composition~~remedy and/or preventive~~ according to claim 9, wherein the pharmaceutical composition is effective for treatment of a chronic disease selected from the group consisting of chronic asthma, glomerular nephritis, obesity, prostate hyperplasia, a disease induced by the progress of arteriosclerosis, and rheumatoid or atopic dermatitis.

17. (currently amended): The pharmaceutical composition~~remedy and/or preventive~~ according to claim 16, wherein the composition is effective for the treatment of~~chronic disease is~~ prostate hyperplasia.

18. (currently amended): The pharmaceutical composition~~remedy and/or~~
~~preventive~~ according to claim 9, wherein the EDG-2 antagonist is saida β -alanine derivative of
formula (I)



wherein A^a is, (1) C1-6 alkylene, (2) C2-6 alkenylene, or (3) C2-6 alkynylene, wherein
 A^a may be substituted with 1-3 of C1-4 alkyl,

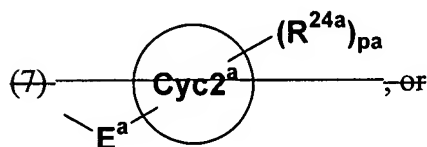
$Cyc1^a$ is, (1) C3-15 carboring, or (2) 3-15 membered heteroring having 1-4 of nitrogen,
1-2 of oxygen and/or 1-2 of sulfur,

R^{1a} is (1) C1-4 alkyl, (2) halogen, (3) cyano, (4) trihalomethyl, (5) OR^{6a} , (6) SR^{7a} ,
(7) $NR^{8a}R^{9a}$, (8) nitro, (9) $COOR^{10a}$, (10) $CONR^{11a}R^{12a}$, (11) $NR^{13a}COR^{14a}$,
(12) $SO_2NR^{15a}R^{16a}$, (13) $NR^{17a}SO_2R^{18a}$, (14) $S(O)R^{19a}$, or (15) SO_2R^{20a} ,

R^{6a} , R^{7a} , R^{8a} , R^{9a} , R^{10a} , R^{11a} , R^{12a} , R^{13a} , R^{14a} , R^{15a} , R^{16a} , R^{17a} , R^{18a} , R^{19a} and R^{20a} are each
independently, (1) hydrogen, or (2) C1-4 alkyl,

R^{2a} and R^{3a} are each independently, (1) C1-4 alkyl, (2) C1-4 alkoxy, or (3) halogen,

~~_____R^{4a} and R^{5a} are each independently, (1) hydrogen, (2) C1-4 alkyl, (3) C2-4 alkenyl, (4) C2-4 alkynyl, (5) C1-4 alkyl substituted with OR^{21a}, (6) C1-4 alkyl substituted with NR^{22a}R^{23a} or~~



~~_____R^{4a} and R^{5a} are taken together with the nitrogen to which they are attached to form a 3-15 membered mono-, bi- or tri-cyclic heteroring, wherein the heteroring represents at least one nitrogen and it may be substituted with C1-4 alkyl substituted with OR^{25a};~~

~~_____R^{21a}, R^{22a}, R^{23a} and R^{25a} are each independently, (1) hydrogen, (2) C1-4 alkyl, (3) C2-6 acyl, or (4) trihaloacetyl;~~

~~_____E^a is (1) a bond, (2) C1-6 alkylene, (3) C2-6 alkenylene, or (4) C2-6 alkynylene, wherein E^a may be substituted with 1-3 of (1) C1-4 alkyl, or (2) C1-4 alkyl substituted with OR^{26a};~~

~~_____R^{26a} is (1) hydrogen, (2) C1-4 alkyl, (3) C2-6 acyl, or (4) trihaloacetyl, Cyc2^a is (1) C3-15 carboring, or (2) 3-15 membered heteroring having 1-4 of nitrogen, 1-2 of oxygen and/or 1-2 of sulfur;~~

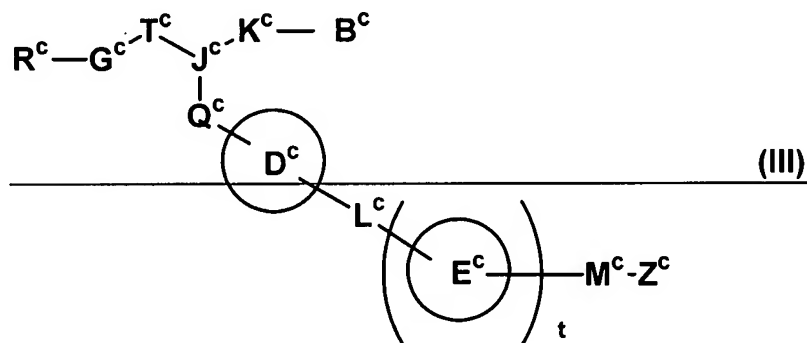
~~_____R^{24a} is (1) C1-4 alkyl, (2) halogen, (3) cyano, (4) trihalomethyl, (5) OR^{27a}, (6) SR^{28a}, (7) NR^{29a}R^{30a}, (8) nitro, (9) COOR^{31a}, (10) CONR^{32a}R^{33a}, (11) NR^{34a}COR^{35a}, (12) SO₂NR^{36a}R^{37a}, (13) NR^{38a}SO₂R^{39a}, (14) S(O)R^{40a}, or (15) SO₂R^{41a};~~

~~_____R^{27a}, R^{28a}, R^{29a}, R^{30a}, R^{31a}, R^{32a}, R^{33a}, R^{34a}, R^{35a}, R^{36a}, R^{37a}, R^{38a}, R^{39a}, R^{40a} and R^{41a} are each independently (1) hydrogen, or (2) C1-4 alkyl;~~

~~ia is 0 or an integer of 1 to 5, ma is 0 or an integer of 1 to 4, and~~
~~na is 0 or an integer of 1 to 4, pa is 0 or an integer of 1 to 5, and~~
~~wherein when ia is 2 or more, R^{1a}'s are the same or different,~~
~~when ma is 2 or more, R^{2a}'s are the same or different,~~
~~when na is 2 or more, R^{3a}'s are the same or different, and~~
~~when pa is 2 or more, they are the same or different, or~~
a prodrug thereof or a salt thereof.

19. (canceled).

20. (currently amended): The pharmaceutical composition ~~remedy and/or~~
~~preventive~~ according to claim 9, wherein the EDG-2 antagonist is at the compound of formula
(III)



~~wherein R^e is optionally substituted aliphatic hydrocarbon or a ring group optionally~~
~~having substituent(s),~~

~~—— G⁶ is a bond or a spacer having a main chain of 1 to 8 atoms,~~

~~—— T⁶ is —CH₂— or a spacer having a main chain of 1 atom having a hydrogen bond accepting group optionally having substituent(s),~~

~~—— J⁶ is nitrogen or carbon,~~

~~—— B⁶ is optionally substituted aliphatic hydrocarbon or a ring group optionally having substituent(s),~~

~~—— K⁶ is (1) a bond or (2) a spacer having a main chain of 1 to 8 atoms which may form a ring together with the substituent of the ring group represented by R⁶, ring D⁶ or the substituent of the ring D⁶;~~

~~—— Q⁶ is (1) a bond or (2) a spacer having a main chain of 1 to 8 atoms which may form a ring together with the ring group represented by R⁶, a substituent of the ring group represented by R⁶, or K⁶;~~

~~—— ring D⁶ is a ring optionally having more substituent(s),~~

~~—— L⁶ is a bond or a spacer having a main chain of 1 to 3 atoms,~~

~~—— ring E⁶ is, a ring group optionally having substituent(s),~~

~~—— M⁶ is a bond or a spacer having a main chain of 1 to 8 atoms,~~

~~—— Z⁶ is an acidic group, and~~

~~—— t is 0 or 1, or~~

a salt thereof.

21. (new): The method according to claim 14, wherein said compound of formula III is one compound selected from the group consisting of a compound of formula (III-1), a compound of formula (III-8) and a compound of formula (III-8-3):

